GP #1614

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Assistant Commissioner for Patents
U.S. Dept. of Commerce / Patent & Trademark Office
Attn: Examiner Dwayne C. Jones, AU 1614
Washington, D.C. 20231

RE: Pat. Application #09/781,491
Clouatre, et al., Methods And Pharmaceutical Preparations For Normalizing Blood Pressure With (–)-Hydroxycitric Acid
Office Action Mailed 11/25/02

Dear Examiner Jones:

The Office Action of 11/25/02 consists of two objections based upon, respectively, Shrivastava, et al. (US Patent #6,221,901) and Littera, et al. (European Patent Application 803,202 A2). Neither of these objections is valid. Not to put too fine a point on matters, the present Office Action directly contradicts the clear language found in Shrivastava, et al., indeed, contradicts the grounds on which that patent was granted. In the case of Littera, et al., the objection put forth in the Office Action was refuted in advance in the text of the current application and flies in the face of twenty years of medical evidence.

Office Action Response Paragraph 7

In rejecting Claims 1 and 4-8 based upon Littera, et al., it is asserted that our application is "clearly anticipated" because the European application teaches a method in which (–)-hydroxycitrate reduces cholesterol and triglycerides, hence is effective in treating hypertension. The problem with this objection is that the claim that reducing cholesterol and triglycerides will assist in treating hypertension is not true. As indicated in our application and in the supporting literature, "β-blockers definitely increase the risk of developing diabetes Type 2, and diuretics may similarly increase this risk. Both classes of drugs may increase insulin resistance, LDL-cholesterol and triglycerides. (Sowers JR, Bakris GL. Antihypertensive therapy and the risk of type 2 diabetes mellitus. N Engl J Med. 2000 Mar 30;342(13):969-70.) (Preuss HG, Burris JF. Adverse metabolic effects of antihypertensive drugs. Implications for treatment. Drug Saf. 1996 Jun;14(6):355-64.)"

If the two major classes of drugs used to treat hypertension themselves increase LDL-cholesterol and triglycerides, it can hardly be deemed "obvious" that reducing these blood fats will lower blood pressure. Hence it cannot be that on the grounds given in the Office Action that our application is "clearly anticipated."

Similarly, from the other side, the claim that reducing LDL-cholesterol and triglycerides will assist in lowering elevated blood pressure has been experimentally refuted any number of times over the last two decades. Direct trials of powerful lipids lowering drugs repeatedly have failed to yield this result. To take but one very recent case, fenofibrate, a powerful lipids lowering agent, did not have a significant effect upon blood pressure even after 12 weeks of intervention.

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(Hodgson JM, Watts GF, Playford DA, Burke V, Croft KD. Coenzyme Q(10) improves blood pressure and glycaemic control: a controlled trial in subjects with type 2 diabetes. Eur J Clin Nutr. 2002 Nov;56(11):1137-42.) This same trial also showed once again that yet another piece of "common knowledge," to wit, that antioxidants lower blood pressure, is also false. CoQ-10 did indeed lower blood pressure, but not via an antioxidant mechanism. A number of antioxidants, including vitamins A and E, actually tend to elevate blood pressure. Clinical evidence refutes the notion that manipulating blood fats *per se* influences blood pressure.

In the Office Action it is indicated that Littera, et al. (p. 2, lines 7-12 and 50-52) propose treating various disorders, including hypertension. But this not the case. First, lines 1- 10 lay out the invention as being one directed toward remedying hypercholesteremia and obesity. Lines 11-12 are very poorly worded and actually say that the invention is efficacious in weight reducing programs aimed at calorie restriction in obese subjects and in the treatment of hypertension. These lines do not claim anti-hypertensive effects with regard to the indicated composition, but rather indicate (correctly) that reducing excess weight lowers blood pressure. Furthermore, there is no reference to hypertension or its treatment in lines 50-52 of Littera, et al.

In light of the above, it would appear that Littera, et al., has no relevance to the current application.

Office Action Response Paragraph 5

The objections based on Shrivastava, et al. would appear to suffer from a number of defects. The most significant of these surely is that the obviousness claim being made in the Office Action is directly denied in the patent itself. If Shrivastava, et al., the authors of the patent upon which the objections are based, deny the points being put in their mouths, it is very hard to understand how the Office Action can assert that what is denied expressly in the issued patent is somehow obvious to one "skilled in the art." Were Shrivastava, et al. not skilled in the art?

Lowenstein in 1973 (US Patent #3,764,692), long before Shrivastava, et al., mentioned many possible salts for (–)-hydroxycitric acid, several of which were actually on the market at the time of the filing of the application by Shrivastava, et al. Trisodium hydroxycitrate, after all, was used in many of the experiments published by Roche Pharmaceutical dating from the 1970s. Therefore, when Shrivastava, et al., indicate explicitly that magnesium hydroxycitrate — a compound which they falsely claim is new to them — has properties not found in present (–)-hydroxycitrate products, Shrivastava, et al. expressly deny what the Office Action is claiming.

Were it the case as claimed in the Office Action that "[a]lthough the prior art reference of Shrivastava, et al. teaches of using the magnesium salt of hydroxycitrate it is well within the level of skill of the artisan to substitute one pharmaceutically acceptable cation for another," then Shrivastava, et al. would not have expressly distinguished their substance from all current hydroxycitric acid salts. This has nothing to do with dosage (Office Action paragraph 11).

In the BACKGROUND OF THE INVENTION, Shrivastava, et al. go to some lengths to indicate that neither (–)-hydroxycitric acid itself nor its other salts have the properties of magnesium (–)-hydroxycitrate. Shrivastava, et al. give a recitation of properties which they consider as being desirable, but not found in present (–)-hydroxycitrate products. As the authors of that patent put it: "It would therefore be desirable to find a product endowed with the

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following properties...." Of course, Shrivastava, et al. claim that they fulfill this need with magnesium (–)-hydroxycitrate. Excluded of necessity are the calcium, sodium and ethylenediamine salts mentioned everywhere in the literature, and, by extension, all salts other than magnesium.

Therefore, on its face it would appear that Shrivastava, et al. themselves expressly deny that "one skilled in the art" would come to the conclusions put forth in the Office Action. Shrivastava, et al. make their claims explicitly for magnesium hydroxycitrate as opposed to hydroxycitric acid itself (as shown in their pharmacological studies) and as opposed to the other hydroxycitric acid salts already in the literature (as stated in their own BACKGROUND OF THE INVENTION). The grounds for rejection found in the Office Action, paragraphs 5 and 11, thus clearly run counter to the language of the very patent upon which they based.

Finally, I must point out once again that Shrivastava, et al. (column 8, lines 30-37) failed to test either magnesium or (–)-hydroxycitric acid as anti-hypertensive agents, as would have been expected — no, required — to support their patent claim. They did not test the former because magnesium had long been known as a hypotensive agent and this would have spoiled their results. They did not test the latter because they had no idea — and no expectation — that (–)-hydroxycitric acid has hypotensive effects. Therefore, the claim of Shrivastava, et al. must be for magnesium (–)-hydroxycitrate sole, that is, for magnesium with hydroxycitric acid as a ligand. This has no implications for other salts of hydroxycitric acid nor for the acid itself.

Shrivastava, et al.'s teaching regarding magnesium hydroxycitrate is analogous to claiming that vitamin E succinate has special properties as opposed to either vitamin E or succinic acid. In the case of vitamin E, a claim for vitamin E succinate does not mean that either vitamin E alone or vitamin E with other ligands (such as acetate) will have the same properties as vitamin E succinate — by the way, acetate does not — hence why would one make such a dubious leap (in the Office Action) with regard to hydroxycitric acid, especially inasmuch as Shrivastava, et al. themselves claim the opposite?

What is obvious is that Shrivastava, et al. relied on the distinction between magnesium hydroxycitrate and all other HCA salts (along with various omissions of prior art) to get their patent in the first place. The simple fact of the matter is that Shrivastava, et al. did not know, let alone teach, that a hypotensive effect is characteristic of hydroxycitric acid. What Shrivastava, et al. do teach is that magnesium is somehow potentiated by using hydroxycitric acid as a ligand. This is all that they teach, and such is reasonably clear simply from reading what they wrote in the patent. It is Clouatre, et al., who discovered that hydroxycitric acid itself reduces elevated blood pressure, possibly via glucocorticoid, insulin, leptin or other mechanisms, and that this quality is passed on to the salts with varying levels of efficacy dependent in part upon uptake.

In short, Littera, et al., has no bearing whatsoever vis-a-vis the current application. As for Shrivastava, et al., that patent cannot be interpreted or extended as presented in the Office Action without directly contradicting the explicit language of the patent itself.

Sincerely,

Dallas L. Clouatre, Ph.D.

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